VOL. 12, No. 2 FEBRUARY 1958

CHRONICLE OF THE WORLD HEALTH ORGANIZATION

CONTENTS

Page

The work of WHO in the field of tuberculosis 31
Results of BCG vaccination in India 36
Training of health physicists 37
Leprosy control in Thailand 39

Epidemiological and Statistical Information

Cholera in 1957 43
Plague in 1957 43
Recent news of the 1957 influenza pandemic 43

Reports of Expert Groups

Measurement of levels of health 45
Use of specifications for pharmaceutical preparations 48
Safety of food additives 52

Health Legislation

Medical specialization: a comparative study 55

Notes and News

Sensitivity reactions to penicillin 57
Effect of intradermal tuberculin tests on BCG-induced allergy 57
Interpretation of tuberculin reactions 58
Economic losses caused by echinococcosis 59
Recent developments in the insecticide-resistance problem 60
A promising outlook for malaria eradication in Southern Rhodesia . . . 60
Meeting on malaria eradication 61
Division of Malaria Eradication established at WHO Headquarters . . . 61
US contribution of $7 million to malaria eradication funds 61

Review of WHO Publications 62

The mention of specific companies or of certain manufacturers' products does not imply that they are endorsed or recommended by the World Health Organization in preference to others of a similar nature which are not mentioned. Proprietary names are distinguished by initial capital letters.

PRINTED IN SWITZERLAND

THE WORK OF WHO IN THE FIELD OF TUBERCULOSIS*

Objectives and organization

Even though some of the problems of tuberculosis control, such as tuberculosis in migrants, refugees and seafarers, are really international in character, the main task is still the control of tuberculosis within each country. The aim of WHO in the field of tuberculosis is therefore to assist governments to make the maximum impact on the tuberculosis problem in their respective countries.

The assistance given may be divided into two main categories, direct and indirect. The former is the responsibility of the appropriate regional office, while the latter is provided by WHO through its Headquarters.

Direct assistance to governments

This may take a variety of forms, which can be grouped conveniently under the following general headings:

General advice on tuberculosis control. This is often given by correspondence or in discussions between government officials and the officers of the regional office. In some cases a WHO consultant may visit the country for a short period; in others a WHO officer is especially assigned to a country for a longer period to give advice on the general control programme or on certain aspects of it.

Projects for teaching, training and demonstration. Up to now, a large part of the direct assistance provided by WHO has come within this category. The projects have consisted partly in establishing so-called " tuberculosis centres " and partly in organizing mass BCG-vaccination campaigns. For such projects WHO makes available specially trained personnel, and often a limited quantity of supplies and equipment. The WHO personnel take an active part in the daily routine work on the projects, but are concerned only with demonstrating how the work should be planned and executed, and with teaching and training national personnel.

Fellowships, and teaching and training courses. In all its work WHO places great emphasis on the training of the personnel who are to occupy key positions in its programmes. If the appropriate training cannot be obtained within the country, fellowships may be granted to suitably qualified people to enable them either to visit one or more countries to see similar work actually in progress, or to attend special courses. WHO also takes an active part in organizing national teaching and training courses—in addition to those connected with the WHO-assisted projects—and may provide assistance in the form of instructors and teachers, especially if the government agrees to a considerable number of foreign students attending a course.

Indirect assistance to governments

It is perhaps difficult to appreciate the value to governments of much of the indirect assistance given by WHO, but a few examples may help to make this clearer.

Mainly through its Tuberculosis Research Office, WHO has made and is still making considerable efforts to find a solution to the problem of how one single intradermal test might be used to determine with a high degree of reliability whether or not an individual has been infected with tubercle bacilli, and to what degree a group of individuals has been thus infected. This problem has still not been solved, but it has been found that the Mantoux test with 5 TU appears to provide the most reliable answer, and this information has been of considerable

* Condensed from a report prepared by Dr Johs. Holm, Chief, Tuberculosis Section, WHO, for the WHO Tuberculosis Workers' Conference, New Delhi, 1957, and afterwards published in *Berita Kementerian Kesehatan Republik Indonesia*, 1957, **6**, 12

assistance to many governments, not only in their BCG campaigns but also in other aspects of tuberculosis control work.

Improvements have also been made in a number of other techniques used in tuberculosis control programmes, for example, the development of simple but reliable methods for detecting tubercle bacilli. In another direction, the makers of X-ray equipment are being urged to produce a simpler, and therefore less expensive, apparatus for chest examination, suitable for use under existing conditions in the tropics.

Most countries are trying to benefit from experience gained and progress made in other countries, and it is one of the functions of WHO to facilitate this exchange of knowledge. The experience gained in one country will not be of full benefit to others, however, unless the results are reported in such a way that they are not only easy to understand but are also comparable with the results obtained in other countries. Some internationally accepted standards are therefore necessary. In December 1955, a study group convened by WHO met in Luxembourg to consider the problem, and it was agreed that WHO should institute a programme of studies with a view to setting up standards to be adopted by countries engaged in tuberculosis control programmes. The working out of standard procedures for tuberculin testing of a population is already nearing completion, and steps are now being taken to achieve standardization of the methods used for the screening of entire population groups for tuberculosis.

Formulation of WHO's technical policy

By " WHO's technical policy " is understood the general approach taken by WHO to a problem such as tuberculosis control, as well as the methods and techniques recommended for dealing with this problem.

Before any recommendations can be made, a considerable amount of knowledge must be amassed about the basic problem and about any methods and techniques that have been used to deal with it in the past. A careful scientific assessment must be made of the experience already gained.

The second step is to evaluate the relative merits of the various possible methods and techniques that might be used. This may necessitate calling on the advice of experienced specialists before a final decision can be made.

In discussing how the knowledge and advice are made available to the organization it is necessary to distinguish between two types of situation: (1) where the necessary knowledge is already in existence, and (2) where the necessary knowledge has to be acquired by instituting special programmes of research.

Access to existing knowledge and experience

With 88 Member States, WHO has unique possibilities of access to knowledge and experience, and also of obtaining expert advice on any matters pertaining to health.

Medical literature. Most of the existing knowledge relating to tuberculosis control, wherever it was acquired, will sooner or later be published in the medical literature. A good part of the recent medical literature is directly available in the WHO library in Geneva.

Conferences. WHO is invited to send official representatives to a large number of conferences and meetings at which matters relating to tuberculosis and tuberculosis control are discussed. One advantage of these meetings is that they frequently provide contacts with specialists from countries which medical officers from WHO Headquarters have little opportunity to visit. In addition to the immediate benefit of obtaining information concerning problems and experience in these countries, such meetings often suggest where to go for useful advice in the future.

Expert Advisory Panel. The Expert Advisory Panel on Tuberculosis at present consists of 28 members from 24 countries. It provides the Organization with the machinery for obtaining existing technical information on any particular subject in the

field of tuberculosis from experts in any part of the world.

Most of the members have extensive knowledge and experience of only one, or a few, of the many topics on which expert advice is needed. In view of the rapid development of new specialized branches of tuberculosis control, such as chemotherapy and chemoprophylaxis, the problems submitted to the Panel will be grouped in future into several categories and the Panel divided into corresponding sub-groups. This does not exclude the possibility that a member of the Panel may be asked to cover more than one category.

Contacts with research institutions

Where new knowledge is accumulating quickly, it is important for WHO to keep in close contact with the research institutions concerned. Concerning the effect of anti-tuberculosis drugs, for example, contact is maintained with such institutions as the Medical Research Council of Great Britain, the United States Public Health Service, the United States Veterans Administration, and Cornell University, New York. Similarly, as regards BCG vaccination it is necessary to keep in touch with the International Children's Centre, Paris, the Rockefeller Institute, New York, and the Research Institute of the Japan Anti-Tuberculosis Association, Tokyo.

Short-term consultants. Short-term consultants are frequently appointed by WHO for periods of a few days or a few weeks to provide expert assistance when decisions on technical policy have to be made. For example, at a meeting of the WHO/UNICEF Joint Committee on Health Policy, UNICEF assistance for the domiciliary treatment of tuberculosis was to be discussed. WHO was asked to make recommendations regarding the anti-tuberculosis drugs to be used for such treatment. In order to assist the Organization in reaching a sound decision, three experts from three different countries in Europe were appointed as short-term consultants.

Study groups. In addition to the expert committees which primarily advise WHO's governing bodies and report to the Executive Board, study groups may be appointed to advise the Director-General on particular problems. These groups consist of a number of experts in the same speciality who meet and then report as a group.

Acquisition of new knowledge

Lack of knowledge is the one big factor that hampers the formulation of a sound technical policy on which to base a programme for the control of tuberculosis. To remedy this situation, WHO is taking an active part in promoting research.

There are several ways in which WHO can initiate a research project, but the basic principle is that, whenever possible, the work should be carried out by other institutions or organizations with WHO's moral support and also, if necessary, financial or other direct assistance. Only when the formulation of technical policy is absolutely dependent on possession of certain information and no other competent institution can be persuaded to investigate the problem, is the research undertaken directly by WHO.

The role of WHO is to recommend projects for research and establish some sort of priority. The next step is to decide which of the following approaches can and should be adopted.

Stimulation and co-ordination of research. In general, an appeal from WHO to undertake research receives a very favourable response, even if the problems to be investigated are outside the immediate field of interest of the person or institution concerned.

Another aspect of the co-ordination of research by WHO is that national feelings often make it difficult for research institutions to co-operate directly across national frontiers. In such cases, WHO can provide a neutral and international meeting ground.

The role played by WHO in the stimulation and co-ordination of research can perhaps best be illustrated by two examples:

1. The need for simpler X-ray equipment for chest examination in tropical countries has already been mentioned. For practical reasons, the research necessary to develop such apparatus can be carried out effectively only by the companies producing chest X-ray equipment. WHO has presented the problem in considerable detail to a number of the largest manufacturers, and several of them have been visited by WHO representatives. In order to give interested companies the best facilities for studying the problem involved and for testing their own equipment under actual field conditions in the tropics, X-ray engineers from these companies have been engaged by WHO to work on some of its projects.

2. Evidence has been obtained from the results of a tuberculosis survey in Africa and from other WHO-assisted projects that tubercle bacilli in tropical countries might not have the same characteristics as the types of tubercle bacilli well known in Europe and North America. Research on this problem was obviously required. WHO has succeeded in obtaining the co-operation of five centres with special experience in tuberculosis bacteriology (four in Europe and one in the USA) in a co-ordinated research project on the biological characteristics and geographical distribution of different types or groups of mycobacteria. WHO has undertaken responsibility for collecting material containing mycobacteria (mainly sputa) from different parts of the world and for sending it to the research centres.

WHO may make a token grant to some of the institutions engaged in such a research project, to assist them in obtaining the necessary funds from their own authorities.

WHO-assisted research. Where more direct assistance is necessary to ensure the carrying out of a research project, WHO usually makes a grant to the institution concerned. In general, the institution also makes a material and financial contribution and it is only in exceptional cases that it is necessary for WHO to pay the total expenses.

An example of WHO-assisted research is the investigation undertaken by the Medical Research Council of Great Britain on the domiciliary chemotherapy of tuberculosis in Madras. The administrative arrangements for such a project are rather complicated, and it is sufficient here to say that they are based on agreements between the Government of India and the WHO Regional Office for South-East Asia, and between the Medical Research Council of Great Britain and WHO. The Medical Research Council personnel working on the project are administratively WHO employees. The Council does not pay any of the expenses of the project in India, and receives a grant from WHO to cover the expenses of the work which is carried out in London in connexion with the project.

WHO-conducted research. When it is decided that WHO should itself conduct research on tuberculosis, this is done by the Tuberculosis Research Office. Almost all the problems that have been taken up by the Tuberculosis Research Office fall within the category of field research in public health. When complementary laboratory research is necessary, the co-operation of the Statens Seruminstitut in Copenhagen is obtained.

As far as field research is concerned, there are two different patterns. Some problems can be studied exclusively in Denmark on the local population. The keeping qualities of BCG vaccine and of tuberculin dilutions, and BCG vaccination of the newborn have been studied in this way. There are obvious advantages in having all the personnel engaged in the research directly under the control of the institution responsible for the project.

On the other hand, many problems can only be studied on the basis of field data collected in the countries where they originate and where WHO's advice and assistance have been requested. The planning of the project and the evaluation of the data can, however, be done wherever is most convenient. For the success of such an operation, it is important not only that the personnel making and recording the field examinations should be properly trained, but also that there should be constant and direct

contact on technical problems between the field personnel and the office in charge of the project, including periodic visits by field personnel to the office and by office personnel to the field.

This procedure has been adopted for the tuberculosis surveys at present being conducted by WHO in Africa. The field data are being collected by two tuberculosis survey teams—one for West Africa and one for East Africa—which administratively are under the WHO Regional Office for Africa. The record cards are then sent to the Tuberculosis Research Office in Copenhagen, where the data are analysed, and where finally the report will be written.

Basic approach to tuberculosis control

It was stated 50 years ago, and has often been repeated since, that the correct approach to tuberculosis control is expressed in the sentence: " Tuberculosis is a social disease with some medical aspects ". On this basis, tuberculosis control would consist mainly in improving social and economic conditions. There is, of course, a close connexion between the standard of living of a community and the magnitude of its tuberculosis problem. In practice, however, this approach implies that no direct control measure is effective, and the description of tuberculosis as a social disease has often been used as the excuse for not taking any active steps to control tuberculosis.

The correct approach, WHO believes, is a dynamic one, based on the knowledge that tuberculosis is a communicable disease. From this it follows that if enough is known about the mechanisms which keep tuberculosis going in a population—the epidemiology of tuberculosis—and about the struggle for survival of the tubercle bacilli, it should be possible to interfere with those mechanisms; and the more intimate this knowledge the better the chance of interfering at the right stage. Control measures must consist in establishing barriers to the natural course of events at points where they can be expected to produce the maximum effect at the minimum cost.

Until about a decade ago tuberculosis control was mainly a clinical problem. Examinations for tuberculosis were usually made only when subjective symptoms of the disease were present. Diagnosis rested on the clinical art of the specially trained physician, and treatment was dictated by the clinical judgment of the tuberculosis specialist, without whom no tuberculosis control programme was conceivable. The scarcity of these specialists was one of the greatest limiting factors in tuberculosis control, another being the expense of establishing and running the institutions necessary for effective treatment. The introduction of new methods of diagnosis and of preventive measures, such as BCG vaccination and treatment with anti-tuberculosis drugs, has changed the situation radically.

Today, chest X-ray films, taken and read by trained technicians, provide a more reliable indication of the presence of pulmonary disease than a physical examination by the best clinician; and since demonstration of tubercle bacilli is considered the only sure basis for diagnosis, the clinician's art is no longer relied upon for case-finding.

Photofluorography has provided a relatively inexpensive method of chest examination, and the introduction of anti-tuberculosis drugs has made it possible to treat infectious cases of pulmonary tuberculosis on a domiciliary basis with standard doses for a standard period, without expensive institutions such as hospitals and sanatoria. Altogether, the increased possibilities have created a demand from the community to be protected against tuberculosis.

RESULTS OF BCG VACCINATION IN INDIA

In 1954, WHO and UNICEF undertook to assess the results obtained in the BCG mass vaccination campaign in progress in India. Ideally, the assessment would have determined the extent to which the vaccinations had prevented tuberculosis, but this would have required that some groups be left unvaccinated to serve as controls—a procedure hardly feasible in a mass campaign. The task was therefore limited to an appraisal of the immediate effects of BCG vaccination measured in terms of the degree of post-vaccination tuberculin allergy acquired and an evaluation of the techniques adopted in the campaign.

The assessment work was undertaken by the WHO/UNICEF South-East Asia Regional BCG Assessment Team and was carried out under the technical direction of the WHO Tuberculosis Research Office (TRO) and in co-operation with the Indian Council of Medical Research. The results of the first nine months of assessment work were published in a preliminary report in the WHO *Bulletin*.[1]

The assessment team returned to India in February 1955 to corroborate the preliminary findings and to study certain aspects of the problems raised. This work was described in a second report in the WHO *Bulletin*.[2] The 1955 assessment revealed that the vaccinations had produced a higher and more uniform level of allergy among schoolchildren than seemed indicated in the preliminary assessment and that the variations in allergy (with some very low levels) observed in 1954 appeared to have been due more to deficiencies in the tuberculin test than defects of vaccine or vaccination techniques.

The Mantoux tuberculin test was used on both occasions, but in the second investigation some modifications were introduced to diminish variations in the potency of the tuberculin dilutions, a factor which has a marked influence on the outcome of the test. Investigations made by the TRO had shown that the potency of tuberculin dilutions may vary considerably from one bottle to another, and that the potency in a partially filled bottle tends to be lower than that in a completely filled bottle. To overcome this difficulty, the 1955 team used four bottles of tuberculin in rotation on each testing day, and only two-thirds of the contents of each bottle. These procedures considerably reduced variations in the results, but further studies on the stability of the tuberculin test are still in progress, as an accurate tuberculin test is indispensable for a valid assessment of the results of BCG vaccination.

Another problem studied was the occurrence of natural non-specific sensitivity to tuberculin in the general population. The studies made in 1955 in Mysore and Madras, like those made in 1954 in neighbouring Travancore-Cochin, indicate that in South India an intradermal injection of 5 TU is not a reliable test for distinguishing persons who have been infected with tuberculosis from those who have not. The large number of natural non-specific reactors (persons with intermediate-size reactions to a standard low dose of tuberculin but presumably uninfected with tuberculosis) invalidates the 5 TU test and probably all tuberculin tests in current use. This widespread non-specific sensitivity is not peculiar to India: it is found in many other tropical countries, such as Burma, the Philippines, Indonesia, Mauritius, Nigeria, East Pakistan, the Sudan and Viet Nam. This inadequacy of the tuberculin test is a serious handicap in tuberculosis control programmes, both from the diagnostic and from the epidemiological points of view, and presents a practical problem of great importance in mass vaccination programmes.

A partial solution of the problem would be to raise the limit of a " positive " reaction to the 5 TU test. The adoption of this provisional solution would mean that a larger

[1] *Bull. Wld Hlth Org.*, 1955, **12**, 101
[2] *Bull. Wld Hlth Org.*, 1957, **17**, 203

proportion of uninfected persons and non-specific reactors to tuberculin would be included in the vaccination programme—but it would also mean the inclusion of more infected persons.

The most satisfactory solution would be to develop a more specific tuberculin test. It may be possible to fractionate tuberculin into components that are specific for infection with *Mycobacterium tuberculosis* and components that are responsible for the non-specific reactions. At the present time, various protein fractions are being studied in order to investigate this possibility.

TRAINING OF HEALTH PHYSICISTS

The development of nuclear reactors during the last 15 years has led to the creation of a new industry which is bringing radio-active hazards on a scale previously unknown. Not only is the number of persons at risk increasing, but the levels of radiation involved are extremely high. The gamma flux of a reactor operating even at a relatively low level is equivalent to that from several tons of radium.

The peculiar properties of ionizing radiations and the elusive nature of the dangers of exposure have created a demand for a new kind of highly trained specialist, the " health physicist ", to co-operate with medical men; such an expert is particularly well qualified to supervise practical measures of radiation protection and to work in conjunction with biologically trained scientists in studying the effect of radiation on life. As Dr Elda E. Anderson of the Oak Ridge National Laboratory, Tennessee, USA, stated recently: " Radiation is silent, unseen, unfelt, its presence made known only by instruments, its damaging effects on the human system frequently developing many years after exposure. Thus matters of radiation safety involve technical considerations requiring specialized and experienced scientists. Hence the need for personnel trained in health physics." Dr Anderson was speaking at the second international training course for health physicists, organized by the WHO Regional Office for Europe, in collaboration with the Belgian Government, at the Centre d'Etudes Nucléaires at Mol, Belgium, from 30 September to 31 October 1957. The course, which was directed by Dr Anderson, was concerned not only with the special techniques that the health physicist must acquire but also with the fundamental principles of radiation protection. It was attended by physicists, engineers, chemists and physicians from 18 countries of Europe and the Eastern Mediterranean Region.[1] Dr Anderson was assisted by Mr Myron F. Fair and Dr L. C. Emerson, both of Oak Ridge. Lectures were also given by Dr W. Claus of the United States Atomic Energy Commission, Dr B. A. J. Lister of the Atomic Energy Research Establishment, Harwell, England, and Dr Per Grande of the Radium Hospital, Oslo, as well as by members of the staff of the Centre d'Etudes Nucléaires.[2] Some of the essential qualifications of the health physicist, discussed by Dr Anderson in her address at the closing ceremony, are summarized below.

Requirements for the health physicist

If the health physicist is to understand the radiation hazard associated with routine reactor operation and with potential reactor accidents, he must have a fundamental knowledge of such questions as the sources of energy in the reactor, the distribution of this energy, the characteristics of the fission products, and reactor instrumentation and control. Furthermore, in order to understand the basis for the maximum permissible external doses and the maximum permissible

[1] Austria, Belgium, Bulgaria, Egypt, France, Federal Republic of Germany, Greece, Iran, Iraq, Italy, Lebanon, Netherlands, Poland, Portugal, Switzerland, Turkey, Union of Soviet Socialist Republics and Yugoslavia

[2] Dr Boulenger, M. Dopchie, Dr Faes, M. Goens, M. Jonghe, M. Marien, M. Schonken and M. Spaepen

concentration of radio-active compounds in the body, the health physicist must be informed about the biological effects of ionizing radiations and the factors on which these effects depend. The primary aim of radiation protection is, and must be, to avoid radiation injury without impeding the useful applications of atomic energy and its valuable by-products, the radio-active isotopes. Consequently, the health physicist must not only be familiar with the principles and techniques of protection, but also learn to put the problem into its proper perspective in relation to science, industry and society.

Permissible levels of radiation

Even the smallest amount of radiation probably has some effect on living human tissue, although at low dosages the damage is not detectable. The risk of undetectable damage cannot therefore be eliminated entirely, but the aim must be to reduce it to a minimum by keeping the level of radiation as low as practicable. This is the purpose of radiation monitoring, the routine measurement of the level of radiation to which the personnel engaged in a particular operation are exposed.

For the health physicist to make effective use of monitoring, however, he must also know what are the maximum permissible levels of radiation. As more and more people are becoming liable to exposure, either occupationally or otherwise, to higher levels of radiation, it is important to establish maximum permissible levels for the population as a whole. Although precise numerical data on the effects of natural background radiations on world populations are still lacking, some recent research suggests that the levels previously allowed may have been too high. Animal experiments indicate that the life span is shortened by large doses of radiation and there is presumptive evidence that smaller doses may have a similar, if less pronounced, effect. Moreover, the accumulated effects of chronic exposure appear to be greater than was thought in the past; and it is believed that some of the increase in leukaemia may be due to increased exposure to radiation. For these reasons, a maximum permissible accumulated dose has now been suggested which corresponds to a maximum permissible dose-rate one-third that previously allowed. Maximum permissible levels of exposure for persons living in the vicinity of nuclear plants and for the population as a whole have also been proposed.

Training programmes

If mankind is to have the benefits of nuclear energy without radiation damage to the worker and the public, it is clear that an adequate supply of personnel well trained in the principles and techniques of radiation protection will be essential. The decision to take an active part in promoting international co-operation in this field was taken by WHO in 1954, and, in November of the following year, the first international training course for health physicists was held at the Karolinska Hospital in Stockholm, also under the direction of Dr E. E. Anderson. It was the success of this course and the urgent need for trained personnel—again stressed at the Ninth World Health Assembly in May 1956—that encouraged the holding of further courses. The European Office of WHO has also awarded fellowships to public-health medical officers to attend a course on radiation protection at Saclay, France, this year, and arranged for a regional course on the public-health aspects of radiation protection to be held, in co-operation with the Atomic Energy Research Establishment, Harwell, England, at Oxford from 6 to 17 January 1958. At the closing ceremony of the second health physics course, Dr P. Dorolle, Deputy Director-General of the World Health Organization, outlined the main features of WHO's atomic energy programme, of which the training courses form only a part. " This programme may seem a modest one, " he stated. " In drawing it up, however, two considerations had to be borne in mind: not to make too great a call on the limited number of experts in this field, and not to encroach upon the terms of reference of the numerous other

organizations concerned with atomic energy. The World Health Organization is, in fact, anxious to continue to co-operate, as it has done in the past, with such international organizations as the United Nations, UNESCO, FAO and ILO, which are also occupied, in their own particular fields, with the applications of atomic energy. Again, as recently emphasized, WHO is ready and willing to co-operate with the new International Atomic Energy Agency which has just been established in Vienna under the auspices of the United Nations. Indeed, WHO believes that it is only by respecting the terms of reference of each organization that it will be possible to assure the maximum benefit for all the peoples of the world, without neglecting the interests of future generations. With regard to its own role, WHO is convinced that, by reason of its Constitution, the composition of its directing organs and its secretariat, as well as the traditions it has maintained and the relations it has established, it is the organization which, in the fascinating field of atomic energy, is best qualified to continue to deal with all matters relating to the protection of health and the medical uses of radiation."

LEPROSY CONTROL IN THAILAND *

During the last few years, a new approach to the treatment of leprosy has been made in Thailand. The narrow view previously taken called for rigorous isolation of all patients in leprosaria. An attempt has been made to get away from this principle and to treat leprosy not as a disease apart but as a general public-health problem, along the lines recommended in the first report of the Expert Committee on Leprosy.[1]

The primary aim of this public-health approach is to lower the incidence of leprosy by mass operations carried out by staff working within the general framework of the health administration of the country and conforming to generally accepted control principles. Any measures which will raise the standards of health of the population such as improvements in nutrition, sanitation and housing, are likely to help in the control of leprosy. On the other hand, because of certain peculiarities—mode of transmission, long incubation period, difficulty of case-finding, comparatively long treatment, need of follow-up of treated patients, rehabilitation, etc.—leprosy poses problems of its own, and many of the public-health measures used in the control of other diseases are inapplicable.

In modern leprosy control programmes, carried out with the assistance of WHO, these difficulties are overcome by proceeding in easy stages and by dividing up the areas where leprosy is endemic into small sections, so that the results can be more readily controlled and evaluated. The following are the main steps recommended for what the Expert Committee called "mass control measures in limited areas":

(1) selection of suitable personnel, with genuine sympathy for and devotion to their patients, followed by a programme of training;

(2) a carefully planned survey of the areas where the control measures are to be instituted;

(3) a concentrated attack on leprosy in the selected areas, with mass chemotherapy of registered leprosy patients.

It was with this type of strategy in mind that a basic agreement was signed in 1949 between the Thai Government, WHO and UNICEF. The first step was taken in 1953 with the appointment of Dr L. Dharmendra as short-term consultant to Thailand, to make a survey of the leprosy conditions of the country and the pilot-project area. On the basis of his report, it was possible to define the objectives of the project and to

* Based on a report prepared by Dr Ramon Miquel, Senior WHO Adviser, Leprosy Project, Thailand

[1] *Wld Hlth Org. techn. Rep. Ser.*, 1953, 71

prepare a plan of operations, taking into account the rural domiciliary approach necessitated by the new policy of treating leprosy as a general public-health problem.

The area selected for the pilot project was Khon Kaen Province in north-eastern Thailand, and, with the assistance of WHO and UNICEF, the plan was put into action by the Thailand Department of Public Health in November 1955. The salient features of the project were: early detection of cases, dispensary and domiciliary treatment, follow-up of cases and contacts, routine bacteriological examinations, health education, and research in collaboration with the existing leprosy institutions. With the experience gained in this project, it was intended to develop a nation-wide programme to bring leprosy under control in all areas where it represents a public-health problem.

By July 1957, when the project had been in operation nearly two years, the following results had been achieved:

1. A complete survey of the whole population of Khon Kaen Province had been carried out, with detection of nearly all cases of leprosy in the area. The survey included systematic examination of all school-children, followed by examination of home contacts of cases found, and house-to-house canvassing as far as possible. Against an original estimate of possibly 1000 cases, a register of 5000 patients was prepared, representing an attack rate of 1 % for the area.

2. All registered patients had been treated, either in out-patient clinics or at home. Treatment was given only twice a month, by oral administration or by intramuscular injection. In the majority of cases, treatment could be given with sufficient regularity and adequate follow-up was possible. On the basis of clinical and bacteriological examinations, the initial results were judged to be satisfactory, and it can therefore be assumed that, by reducing the sources of infection, good protection has been offered to the population exposed to contact.

3. The success of the pilot project has demonstrated that the public-health approach to leprosy control is effective and technically feasible for Thailand. The 25 members of the project staff—1 national medical officer, 1 WHO expert leprologist, 3 sanitarians and 20 lay health workers—were found adequate to cover a population of about 600 000 and to deal with some 5000 cases of leprosy and their contacts.

The project also showed that, in addition to the adoption of a technically sound control method, three factors are of importance for the success of any campaign:

(1) availability of funds;

(2) the right type of personnel;

(3) co-operation from the public, including local authorities and leprosy patients.

In Thailand the government budget is adequate for salaries and supplies, the national staff has generally proved to be efficient, and the patients themselves are co-operative. It has therefore been possible to proceed with plans for a nation-wide programme based on the results of the pilot project.

The new plan, prepared by the Thailand Department of Public Health with the assistance of WHO and UNICEF, is due to come into operation in 1958 and will be extended, step by step, to cover all areas in Thailand where leprosy constitutes a public-health problem. It is estimated that it will take 10 years to complete this process. The programme has been conceived in three stages, which will be applied successively to each of the limited areas as they are brought into the scheme:

(1) the operational phase;

(2) the phase of consolidation;

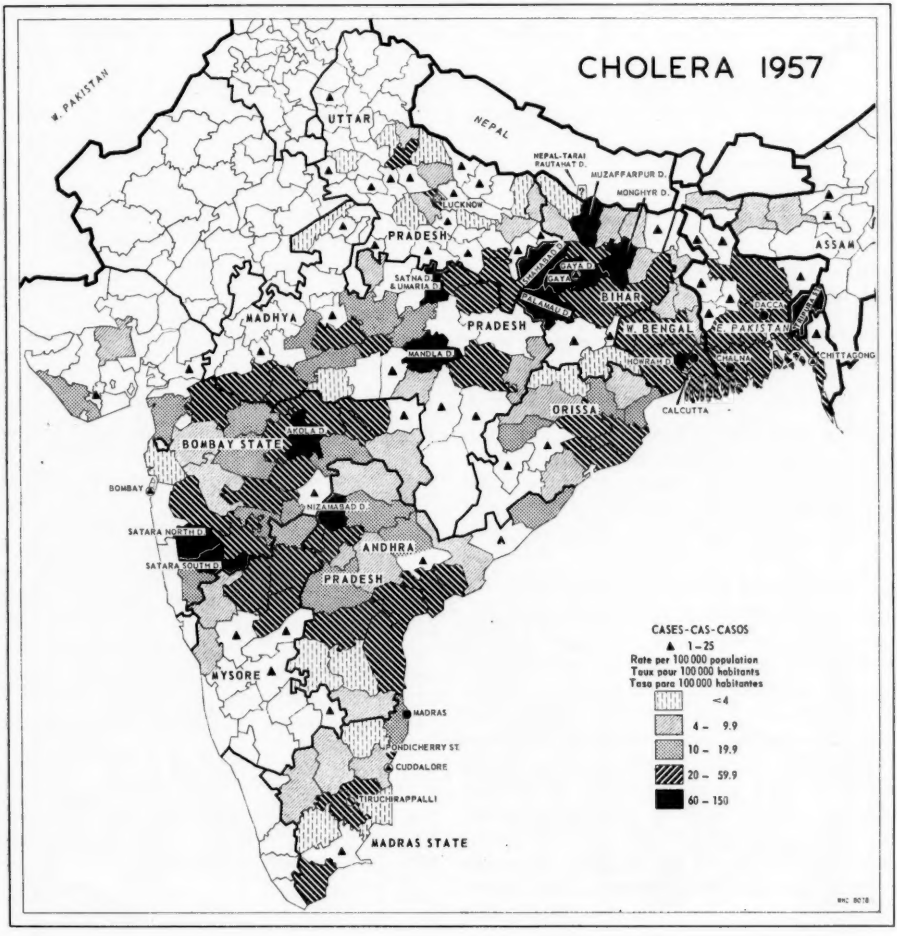
(3) the phase of maintenance or integration.

In the operational phase, a concentrated attack will be made on the area by a specialized team, along the lines of the pilot project already carried out in Khon Kaen. It is expected that the first two phases will last four years. In the second phase, there will be partial integration into the existing public-health services, but a partial retention of the specialized staff. Finally, in the third phase,

leprosy control will be completely integrated into the work of the general public-health services.

One of the most encouraging features of the pilot project is that public co-operation in the leprosy control programmes was found to be readily forthcoming if the right approach is made. The age-old stigma attaching to leprosy is being steadily overcome and people are slowly beginning to realise that it is no longer an incurable disease. If the government makes persistent efforts to bring relief as near to the home of the patient as possible, there is no doubt that the control of leprosy in rural areas will prove a practical proposition.

Epidemiological and Statistical Information



PLAGUE IN 1957

CHOLERA IN 1957

About 60 000 cases of cholera were officially notified in 1957 as compared with 66 000 in 1956. With the exception of six suspected cases in Cambodia and ten cases in Burma, all cases have occurred in India and in East Pakistan. This information is contained in a note on the world cholera situation which appears in a recent issue of the WHO *Weekly Epidemiological Record* (No. 3, 1958).

The map on page 41 shows the incidence of cholera by district in India and East Pakistan in 1957. West Bengal and East Pakistan accounted for one quarter of the reported cases, Bihar and Uttar Pradesh also for one quarter, while the remaining cases were reported in the central and south-eastern parts of India.

PLAGUE IN 1957

According to information contained in the WHO *Weekly Epidemiological Record* (No. 4, 1958), only 514 cases of plague were officially notified throughout the world in 1957, as compared with 670 in 1956, and 1228 in 1955. The 1957 figure is the lowest for any year since the beginning of the century; this is accounted for by the unusually small number of cases in India (44). As shown on the map on page 42, the other principal foci of the disease in 1957 were Burma (198 cases), Ecuador (72 cases), Madagascar (57 cases), the Belgian Congo (35 cases) and Peru (31 cases).

RECENT NEWS OF THE 1957 INFLUENZA PANDEMIC

The influenza pandemic seems to be on the decline. This conclusion is drawn from reports reaching WHO since November 1957. Among information received recently are some figures from Japan, which already had a severe influenza epidemic last summer. A second, milder epidemic occurred in November, particularly in those areas that had been lightly affected by the earlier outbreak. During the first epidemic, the attack rate varied widely in different parts of Japan, ranging from 0% to 93%. The total deaths attributed to influenza—excluding those from pneumonia or bronchitis—were as follows:

Month	*Deaths*	*Month*	*Deaths*
May	34	September *	124
June	518	October *	149
July	793	November *	302
August	297		

* Provisional figures

Antibody response

A lack of specificity in antibody response after infection with the 1957 Asian strain has been noted by many specialists, and the following note appeared in the *Communicable Disease Center Influenza Surveillance Report*, No. 27:

" It has been known for many years that antibody increases measured by complement-fixation test with viral antigens from allantoic fluids are not specific for strain or sub-group within the broad immunologic type. It is not surprising, therefore, to learn that recent complement-fixation tests using antigen prepared with A/Denver/1/57, A/Spirup/48, A/PR8/34, and other older Type A strains are often positive in the presence of Asian strain infection. Similarly, antibody increases measured with the A/Asian/57 CF antigen would not necessarily be due to infection with an Asian strain.

"The hemagglutination inhibition test appears to be somewhat more specific. However, even with it, antibody increase can occasionally be detected using strains which were prevalent some time ago but are not responsible for the present infection. The observation has been made repeatedly that patients from whom Asian isolates have been obtained may produce antibody more readily detected with an A/Denver/57 or some older strain than with an Asian strain. This phenomenon is very similar to that described several years ago and epitomized by Davenport and Hennessy as the 'Doctrine of Original Antigenic Sin'."[1]

These two authors were able to show, in fact, that the dominant antigens of the strains of influenza virus responsible for primary infections in childhood exert a persistent "orienting" effect on the production of antibody throughout the life of the individual. Monovalent influenza virus vaccines were given to persons in three different age-groups. It was found that, irrespective of the strain of virus used, children born after 1943 responded with a rise in the titre of A-prime antibody, young recruits with a rise in type A antibody, and persons over 30 years of age with an increase in antibodies to strains of swine influenza. This antibody response to heterotypic viruses appears to reflect the original exposure of the individual to certain types of virus, rather than serological cross-reactivity to several different types. By making use of this phenomenon, it should be possible to characterize each age-group of the population by a serological index which could be employed as an aid to the epidemiological study of the different variants of the influenza virus.

[1] Davenport, F. M. & Hennessy, A. V. (1956) *J. exp. Med.*, **104**, 85

Type of virus responsible for the 1957 epidemics

According to recent information, the Influenza Center at Montgomery, Alabama, USA, has identified 232 strains of influenza virus received from 53 laboratories during the past few months. Only 4 of these were type B; the remainder were all closely related to the strain A/Asian/Japan/305/57. It is thus evident that older strains were not responsible for the majority of the epidemics occurring in 1957. The report of the centre stresses the fact that, used alone, neither the complement-fixation test nor the haemagglutination-inhibition test enables a virus to be identified with certainty. When only the HI test was used, as many as 40% of known Asian strain infections went undetected. By combining the two tests, a much greater degree of sensitivity and specificity is possible, but absolute proof of the identity of the strain depends on isolation of the virus.

* * *

During the last few months, the network of WHO influenza centres[2] has again been expanded, and the addition of two new laboratories in Moscow, USSR, and Warsaw, Poland, has recently been announced. These centres continue to collect and transmit information concerning the progress of the epidemics and their virological and immunological aspects.

[2] A map showing the sites of the various WHO influenza centres was published in *Chron. Wld Hlth Org.*, 1957, **11**, 280.

Reports of Expert Groups

MEASUREMENT OF LEVELS OF HEALTH

Since the raising of living standards to the maximum possible level is among the principal aims of the international organizations concerned with economic and social matters, it is desirable that these standards should be accurately determined. Living conditions, however, are at present so different throughout the world that it is difficult to set a single standard for all countries, or even for all the inhabitants of one and the same country.

Nevertheless, there is no doubt that each social group has a level of living which is affected for better or for worse by changes in economic and social conditions. Bearing this fact in mind, various international organizations decided, in 1949, to assess the needs of economically under-developed countries, with a view to better planning of programmes of assistance to these countries and subsequent evaluation of the results. They recommended that a clear and internationally acceptable definition of the concept of " standards of living " should be established, and that adequate methods for the measurement of these standards should be found.

In 1952, the United Nations Economic and Social Council asked the Secretary General to convene an Expert Committee on International Definition and Measurement of Standards and Levels of Living. This Committee, which met in New York in 1953, included representatives of the United Nations, ILO, UNESCO, FAO and WHO.[1]

As it is impossible to establish an index of living for international application, the Committee suggested that an analysis be made of various representative and generally accepted components, and various statistical indicators for these components. It recommended that the following twelve components should be taken into account: health, including demographic conditions; food and nutrition; education, including literacy and skills; conditions of work; employment situation; aggregate consumption and savings; transportation; housing, including household facilities; clothing; recreation and entertainment; social security; and human freedoms. Health heads the list as being a fundamental factor in levels of living and as being more or less closely related to the other components.

The World Health Organization was asked to study the components relating to health, and the corresponding indicators. Since its foundation, WHO has been endeavouring to improve methods of assessing community health in continuation of the work on health indicators already carried out by the Health Organization of the League of Nations.

In February 1955, Sir Andrew Davidson was invited by the Organization to undertake a preliminary study of the problem. This study served as a basis of discussion for the Study Group on Measurement of Levels of Health, which met in Geneva in October 1955. The report of this group is summarized below.[2]

Sources of data on levels of health

The measurement of the level of health of a community is one of the most formidable problems confronting the health administrator, and his task would be immensely facilitated if he had at his disposal a set of reliable health indicators. Up to the present, he has had to rely on analysis of vital statistics, epidemiological information, data collected from health surveys, and special methods

[1] United Nations (1954) *Report on the international definition and measurement of standards and levels of living*, New York (E/CN.3/179-E/CN.5/299)

[2] WHO Study Group on the Measurement of Levels of Health (1957) *Report* (*Wld Hlth Org. techn. Rep. Ser.*, No. 137), 29 pages. Price: 1/9, $0.30, Sw. fr. 1. Also published in French and Spanish.

for the evaluation of health activities [3] but he has been without any satisfactory indicators of all three aspects of health laid down in the WHO Constitution, that is, " physical, mental and social well-being ".

As a rule, investigations into the health of a community are based on the study of mortality rates, expectation of life and incidence of communicable diseases, whose variations are considered as an indication of progress or of retrogression as the case may be. It has been argued that a drop in the mortality rate and an increase in the expectation of life do not necessarily reflect an improvement in the general level of health. Nevertheless, there is usually a positive correlation between the level of health and length of life.

Reliable mortality figures have the merit of enabling comparisons to be made between one period and another and between one country and another, thus providing useful indications of the changes which have taken place in community health and the factors affecting it.

In this connexion, it is interesting to note variations in infant mortality rates, but it should not be forgotten that in many countries the considerable drop in deaths in the early age-groups has not brought with it any parallel improvement in the health of the community as a whole, and that the aim is not only to add years to life but also to improve health during those years.

Statistics relating to notifiable diseases have also been used for the evaluation of health levels. Such statistics do not lend themselves to international comparison, however, as they vary too much in their reliability.

To be fairly comprehensive, a list of morbidity statistics would include records of sickness among persons covered by social security schemes, adult incapacity, social survey of sickness of all forms, hospital in-patient and out-patient records, general practitioner studies and the more routine surveys of population groups (school-children, recruits, etc.). Analysis of morbidity statistics makes it possible to ascertain the nature and extent of diseases, and to study variations in prevalence which may throw light on the etiology and predisposing factors. This is one of the reasons why WHO and the National Vital and Health Statistics Committees are endeavouring to standardize methods of ascertaining morbidity in order to make possible the international comparison of levels of health. Up to the present, assessment of health has consisted in the measurement of disease, but specialized surveys, like those made in connexion with nutrition and housing, are a more direct approach to the problem of finding positive indicators for the measurement of health.

Various types of health indicators

The Study Group classified health indicators in three categories, according to whether they refer to (*a*) the level of individual or collective health in an area (vital statistics, nutrition, etc.); (*b*) physical environmental conditions in the area concerned; (*c*) health services and activities for the improvement of health conditions (availability and use of hospitals, physicians and other health personnel). An alternative way of classifying these health indicators would be according to the type of study employed: micro-analytical (study of the individual) or macro-analytical (study of families, communities, or whole countries). Irrespective of the unit studied and the method employed, *comprehensive indicators* might be established for the various aspects or groups of aspects of the problem, and *specific indicators* for particular aspects of the problem or for a single factor.

In the absence of sufficient information on which to base particular *comprehensive indicators*, the group did not make any categorical recommendations in this respect, although it emphasized the practical value of the following: (*a*) *proportional mortality ratio* ; (*b*) *expectation of life* ; (*c*) *crude death rate.*

The *proportional mortality ratio* (*number of deaths among persons of 50 years and over*

[3] American Public Health Association, Committee on Administrative Practice (1955) *Guide to a community health study*, revised, New York

as a percentage of total deaths) was suggested by S. Swaroop and K. Uemura.[4] It is clear that if all persons survived up to 50, then the index would be 100; if no one reached that age the index would be zero. This method lends itself to international comparison; the necessary data are also easy to collect, and it provides an effective instrument for the study of levels and tendencies. The Group drew attention to the possibility that " the percentage of deaths under five years to total deaths may well express the toll of communicable diseases " and recommended that studies on this indicator should be continued.

Expectation of life at the age of one year can also serve as a comprehensive indicator, the infant mortality below twelve months being included among the specific indicators. In view of the fact that expectation of life is determined in relation to census periods, which are generally spaced at ten-year intervals, it is particularly suitable for comparisons covering long periods of time.

The *crude death rate* is based on the total number of deaths registered annually per 1000 inhabitants. Although this is not a very sensitive indicator, in many countries birth and death registers may be the only available sources of data.

The category of *specific indicators* includes: (*a*) *infant mortality* ; (*b*) *deaths from communicable diseases per 100 000 inhabitants* ; (*c*) *data concerning health services and activities.*

The *infant mortality rate* has always been considered as an important indicator of the level of health. Deaths among infants of 1-11 months may be affected by social and environmental conditions, but to reflect this a refinement of statistics is needed which is rare in the less developed countries. For general use, deaths under one year per 1000 live births should still be considered as a useful indicator.

With regard to *deaths from communicable diseases*, a high death rate usually reflects a low level of living. For purposes of comparison, all infective and parasitic diseases listed in Section I of the Detailed International Lists of Diseases, Injuries and Causes of Death, or under the corresponding headings in the Intermediate or Abridged Lists, should be used or, if this is not feasible, the diseases listed for the total mortality figure should be specified.

With respect to *data concerning health services and activities*, it would be useful to have information regarding the number and geographical distribution of physicians and other health personnel, their level of training and qualifications, and the extent to which their services are used. It must be recognized, however, that numerical data on physicians and hospital beds are not always an exact indication of the real health service facilities available in a given zone, which can best be assessed by means of sample surveys. This type of information on health services and activities is also unsuitable as an indicator of the results of mass campaigns by mobile teams, such as those conducted in certain African territories.

Possible new indicators

The provision of *protected water supplies* and of *proper facilities for disposal of excreta* might be useful indicators for assessing *environmental conditions*, provided that the extent to which the facilities are actually used is also ascertained. Special studies would also make it possible to determine the influence of ethnological factors.

Knowledge concerning the measurement of *mental health*, *nutrition* and *health aspects of housing* has not yet reached a stage where the Group felt able to suggest indicators suitable for world-wide application. In this connexion, and also with respect to the *social factors* which influence health, the Group suggested that the international organizations, the national services and the research institutes should undertake surveys of family living conditions, and that sociologists and ethnologists should study the various social structures and systems, particularly in the under-developed regions.

[4] See *Bull. Wld Hlth Org.*, 1957, 17, 439.

Surveys of representative population groups

The Group recommended the carrying out of special sample surveys to obtain detailed information on which new and more satisfactory indicators could be based. In the under-developed areas such surveys could provide vital and health statistics which would constitute a basis for registration systems. This is a method to be recommended because it is not costly and the data collected can be rapidly analysed. Moreover, data obtained direct from a representative population group are nearly always more reliable than those taken from a general register.

In accordance with the report of the Expert Committee on International Definition and Measurement of Standards and Levels of Living, already referred to above, two types of sample survey were proposed, i.e., the multi-purpose and the special-purpose survey. The former would cover the various aspects of individual or community living (nutrition, consumer goods, employment, education, transport, social security, etc.) and would provide a great deal of interesting information on health. This method is particularly suitable for multi-phase investigations in a single area. The first phase would consist in a general survey of family living conditions. On the basis of the information obtained, it would be possible, by applying the principles of probability, to select suitable fractions of the original first-phase sample for the collection of more detailed and technical information, which could then be used to select a third-phase sample, and so on. The data on purely health factors may be classified in two large groups, depending upon whether they relate to *total prevalence* or to *incidence of new cases*. Information on prevalence can be obtained by general census methods whereas incidence data must be reported at the time of occurrence if they are to be accurate.

In a *prevalence* study, the following factors must be determined: population of the zone to be surveyed; proportion of the population sick at a given moment; number of houses and proportion with adequate water supply and excreta disposal facilities.

To obtain data on *incidence*, it is necessary to compile a history of happenings previous to the survey, or else to carry out repeated surveys in the same community. A third method is to collect information on previous sickness experience in each age-group, preferably using objective tests indicating exposure to certain diseases (for example, the tuberculin or Schick test) and serological examination (such as sero-protection against yellow fever and the Wassermann test). In interpreting such tests, due attention must be paid, of course, to any immunity induced by vaccination. A variant of this method is to obtain a history of past infections according to age and, through study of the cumulative number of cases in the different age-groups, to arrive at a picture of the morbidity and severity of a particular communicable disease in the population group under study.

Annex 2 of the report of the Study Group on the Measurement of Levels of Health gives three sources of information on health statistics and morbidity surveys: WHO periodical publications containing mortality and morbidity data; other WHO publications and documents on morbidity statistics and, lastly, various publications on national morbidity sample surveys.

USE OF SPECIFICATIONS FOR PHARMACEUTICAL PREPARATIONS

Present position

During recent years, scores of new medicinal substances have been introduced annually into the materia medica, whereas twenty years ago the number was relatively small and five to ten years might elapse between the development of a new drug and its general use. The marketing of new medicinal substances, which often find favour with the public as soon as they are available, may

involve a certain risk to public health if the properties of the drugs are not adequately examined.

By the publication of volumes I and II of the first edition of the International Pharmacopoeia, WHO has provided specifications to be used in the examination of a large number of pharmaceutical preparations. A new step was taken recently, when WHO convened a Study Group on the Use of Specifications for Pharmaceutical Preparations, the report of which has just appeared.[1]

In opening the meeting of this Group, the Director-General of WHO stressed that " it was the first time that a study group had been convened to deal with the methods used for the examination of pharmaceutical preparations in different countries and to study principles which could be of help to national health departments . . ."

World-wide interest has been aroused by this problem, as shown by the information reviewed by the Group. Thus, as early as 1945, the Pan-American Sanitary Organization undertook the study of ways and means of improving food, drug and cosmetic control services in the Americas. The registration of pharmaceutical preparations in the different countries of the Americas was also discussed in 1955 at the General Assembly of the Pan-American Medical Federation. Under the auspices of the International Pharmaceutical Federation, a meeting of directors of laboratories for the control of medicaments has taken place every year since 1947, at which views are exchanged on assay methods used to examine pharmaceutical preparations, as well as on procedures and administrative arrangements. The Pharmaceutical Products Sub-Committee of the Western European Union, which has met regularly for some years, has submitted reports aimed at standardizing the methods of determination of certain characteristics (melting-point, limits of impurities) recommended in different countries, and at obtaining greater uniformity in the classification of poisons, etc. The Pharmaceutical Union of the Arab League also discussed the examination of pharmaceutical preparations in 1955.

WHO has already made a contribution to solving this problem by publishing the first International Pharmacopoeia, the two volumes of which include specifications for more than 400 pharmaceutical preparations in international commerce. The Organization has thus given practical assistance to countries without a national pharmacopoeia, as well as to other countries in the preparation of their national specifications. Furthermore, lists of proposed international non-proprietary names for important pharmaceutical preparations are also published from time to time, and are of considerable help in preventing the confusion caused by a multiplicity of common names for the same preparation. It was agreed that the Group would examine what further contribution would be most useful in these fields, with the collaboration of national, international and commercial institutions.

The examination of pharmaceutical preparations—aims and methods

The purpose of the measures suggested is to protect the consumer and provide for the examination of new preparations as they are placed on the market. It is important that sufficient information should be obtained as quickly as possible.

The examination of pharmaceutical preparations calls for a detailed and precise knowledge of many thousands of products. Consequently, it is almost impossible for any one organization to be familiar with all the problems involved. At present, a large number of the national pharmacopoeias are inadequate for reference purposes and, in many cases, the inclusion of all substances of therapeutic interest in the current edition is impossible, since the preparation and revision of such books require much time and the collaboration of many groups of scientists. Thus, it may happen that specifications for the examination of a substance do not appear in an official book (pharmacopoeia, codex, national formulary) until use of the prepara-

[1] WHO Study Group on the Use of Specifications for Pharmaceutical Preparations (1957) *Report* (*Wld Hlth Org. techn. Rep. Ser.*, No. 138), 29 pages. Price: 1/9, $0.30, Sw. fr. 1. Also published in French and Spanish.

tion is already on the wane. It is true that much information may be found in scientific publications, but the literature is so voluminous and in so many languages that it is almost impossible for those responsible for the control of pharmaceutical preparations to keep abreast of everything that is being published.

Possible future role of WHO

In view of this position, the Group considered a suggestion for the establishment within WHO of a service responsible for obtaining, examining, collating and distributing reference data on new pharmaceutical preparations. To be of the greatest value, such information would have to be made available rapidly. The Group therefore felt it advisable to secure the collaboration of the pharmaceutical industry, either directly or through the members of the Expert Advisory Panel on the International Pharmacopoeia and Pharmaceutical Preparations and other specialists, or through pharmacopoeia commissions, health administrations and other authorities, as in the case of non-proprietary names. On the basis of the information collected, WHO would compile information sheets. These would be distributed to Member States and to members of the Expert Advisory Panel, as well as to other specialists and to control laboratories. The information sheets would give details concerning the chemical formula and molecular weight, physical properties (melting-point, boiling-point, refractive index, optical rotation, etc.), solubility, identification, assay methods for the pure substance and for pharmaceutical preparations manufactured from it, purity tests, stability, storage of the substance and of its pharmaceutical preparations, pharmacology and relevant literature references.

The terms of reference of the Group also included the study of " problems connected with the introduction of new pharmaceutical preparations of therapeutic interest ", and in addition to this question consideration was given to the various aspects of the organization of a national control authority.

Principles to be followed in introducing a pharmaceutical preparation

The Group examined the general principles on which the introduction of a pharmaceutical preparation should be based and found that the relevant regulations differed widely from one country to another. After reviewing the requirements in force in various countries, the Group was of the opinion that the following data might be of value to the authorities responsible for public health:

(*a*) the qualitative and quantitative composition declared in the commonly accepted nomenclature;

(*b*) details of analytical methods and possibly certain useful indications on the method of preparation;

(*c*) physico-chemical constants, if not already known;

(*d*) the therapeutic indications and dosage;

(*e*) the recommended method of selling (prescription, etc.);

(*f*) samples in sufficient quantity for analysis;

(*g*) information concerning label, package and publicity (advertising).

If a speciality contains substances, or combinations of substances, the action of which is not generally known, additional information may be required such as:

(*h*) publications or documents regarding the pharmacological action of the substance and its toxicity, clinical reports on its therapeutic efficacy and side-effects.

The Group felt that study of the legislation in force in different countries should be continued, and that subsequent meetings should consider how this legislation could be simplified and made more uniform, in order to reduce obstacles to international commerce while still fully protecting public health.

Organization of a national control authority

Administration

In most countries, the government itself assumes responsibility for the application of

specifications for pharmaceutical specialities, but in some countries responsibility has been delegated to professional groups, such as national pharmaceutical associations. The government administration may have the laboratory tests and other work carried out in government laboratories, in university departments or in other scientific institutes. It is advisable for the administrator to be solely responsible for the work done, and for the responsibilities of any organization of this nature to be clearly defined. In a small country, savings in personnel and equipment may be effected by installing the administration and laboratory services in one centre. In larger countries, it will usually be more convenient and less time-consuming if regional laboratories are established in the large urban centres. It is often advisable to obtain the views of outside consultants, or possibly of special commissions comprising professors of pharmacy, pharmacology and medicine, as well as members of the scientific and technical staff of firms manufacturing pharmaceutical or chemical products.

Scientific services

In the past, specifications for pharmaceuticals have been based largely on physical and chemical tests such as melting-point, specific rotation and qualitative reactions. In recent years, new tests have been introduced, however, and new techniques developed for the identification of chemical substances and estimation of their purity, e.g. X-ray diffraction, determination of crystallographic characteristics, infra-red absorption spectra, the use of ion-exchange resins, counter-current extraction, chromatographic separation, etc. Use of these techniques calls for specialized personnel.

Staff of a control laboratory

The head of the service in the chemistry and physical chemistry department should be a specialist in pharmaceutical chemistry and be well versed in the many fields of analytical chemistry. He should be familiar with current physico-chemical methods and have a good understanding of pharmacology and physiology.

The analyst should be an adequately trained chemist or pharmacist, proficient in the analysis of preparations for which methods are given in the pharmacopoeia or other official books. After a period of training, he will learn, under the direction of the head of the service, how to work out methods for separating constituents and to choose the best assay technique. Analysts should be selected not only for their basic knowledge, but also for their ability to handle instruments and apparatus.

Laboratory technicians may also be employed, working under the supervision of the analyst, and can relieve him of certain routine operations, such as distillations, extractions, etc.

Fellowships

It is advisable for fellows to make a definite choice of the branch which they wish to study, for it is difficult for the same person to acquire, in a limited time, technical training in the control both of pharmaceuticals and of food. Fellows who intend to carry out laboratory techniques should spend several months in the institute which they are visiting and be given an opportunity to take part in the everyday routine work. Fellows mainly interested in administration and organization could limit their visits to a much shorter period.

Control of pharmaceutical preparations at the time of manufacture

In most countries, the number of preparations sold is so large that the control laboratory cannot examine them all within any reasonable period of time. It is impossible for any country to have sufficient staff to examine every batch of every preparation sold. A few figures will make the extent of the problem clear: in Canada, for example, there are about 26 000 pharmaceutical preparations on the market. If only two batches of each of these are manufactured annually, this calls for 52 000 analyses every year, some

of them very complicated. This is clearly beyond the capacity of an official control laboratory. Thus, an important step which can be taken by the authorities dealing with the examination of pharmaceutical preparations is to arrange for the inspection of pharmaceutical manufacturing plants, with a view to ensuring that they exercise proper control at all stages of manufacture, beginning with the raw materials and proceeding through the production stage to the final pharmaceutical form. Control of the labelling is also very important. When a manufacturer does not have a suitable control system, it may be necessary, in some countries, to give detailed advice on how to set one up.

SAFETY OF FOOD ADDITIVES

Among the many public-health problems of direct concern to everyone, few have been more neglected than the safety of food additives.[1] A wide variety of additives are in use today on a large scale as preservatives, antiseptics, flavouring, colouring and emulsifying agents, etc. In countries with a high standard of living, the use of such substances makes it possible to satisfy the demand for highly attractive foods and a wide choice at all seasons, including foods imported from distant producing areas. In less developed countries, many of which have tropical or sub-tropical climates, but lack modern storage facilities, food additives can be of great value in preventing wastage of seasonal surpluses. From the economic point of view, therefore, food additives serve an extremely useful purpose, but they have their dangers. Not only can they be used by an unscrupulous manufacturer to mask deficiencies in the quality of his product, but they may sometimes prove toxic to the consumer or reduce the nutritional value of the food to which they are added.

For these reasons, there is an urgent need for effective control to be exercised over the use of food additives. In some countries, legislation has already been introduced, but the problem is obviously one requiring international action, particularly in view of the large and ever-increasing volume of international trade in foods treated with additives.

[1] As proposed by the Joint FAO/WHO Expert Committee on Nutrition, this term is used here to denote " non-nutritive substances which are added intentionally to food, generally in small quantities, to improve its appearance, flavour, texture, or storage properties ". See *Wld Hlth Org. techn. Rep. Ser.*, 1955, 97.

Some general principles

At the suggestion of the Joint FAO/WHO Expert Committee on Nutrition, a conference was held in 1955 to see what contribution FAO and WHO could make to the solution of this problem.[2] The conference recommended the setting up of a Joint FAO/WHO Expert Committee on Food Additives to formulate general principles governing the use and control of the substances in question.

The first report [3] of this Committee contained a list of the purposes for which the use of food additives might be considered justified. Before the use of a new food additive is authorized, clear evidence should be available that it will be of benefit to the consumer and that there is no foreseeable risk of harmful effects. The Committee emphasized the importance of estimating the probable rate of consumption when assessing the danger of toxic effects, and the need to exclude the presence of harmful impurities by establishing specifications of purity, defining the substance in chemical and physical terms. Certain administrative measures were outlined which were considered suitable for ensuring the effective control of treated foodstuffs.

At a meeting of the Joint FAO/WHO Expert Committee on Food Additives in June 1957, toxicological procedures were considered in detail. A report has been prepared which is intended to give " a general picture of the type of data that should be

[2] *Wld Hlth Org. techn. Rep. Ser.*, 1956, 107

[3] *Wld Hlth Org. techn. Rep. Ser.*, 1957, 129

available about any additive before its use in food is officially approved ".[4]

It should be noted that the tests proposed by the Committee are not concerned only with the absolute toxicities of the substances examined but are designed with a view to establishing the non-toxicity of these substances under the conditions in which they are expected to be used. Since additives may be taken over the greater part of a lifetime, this means that prolonged tests are essential to rule out the possibility of long-term, cumulative effects. The doses fed to experimental animals must also be much higher than the amounts that will be added to food for human consumption, in order to compensate for the shorter life-span. In view of the great diversity of substances used as food additives, both as regards composition and purpose, the Committee considered that it would be undesirable, if not impossible, to lay down standard experimental procedures for universal adoption; the methods described are therefore to be regarded only as general recommendations. Great emphasis was laid on the need for supporting further research work that might lead to an improvement in the methods available for establishing the safety of a food additive.

Preliminary examination

Before toxicity tests are undertaken, the investigator must be satisfied that the material submitted for examination is physically and chemically identical with the material that will be used commercially. The Committee endorsed the view, expressed in its first report, that FAO and WHO should establish specifications for the more important food additives. Impurities may sometimes represent a greater health hazard than the additive itself, and it is therefore important to know their nature and quantity. A knowledge of the physical and chemical properties of the substance may also provide a guide to the design of the subsequent animal experiments.

[4] Joint FAO/WHO Expert Committee on Food Additives (1958) *Second report : Procedures for the testing of food additives in order to establish their safety for use* (*Wld Hlth Org. techn. Rep. Ser.*, No. 144). Price: 1/9, $0.30, Sw. fr. 1. Also published in French and Spanish.

Finally, it must be remembered that food additives often cause changes in the properties of the food with which they are mixed, particularly on long storage or during cooking. It is therefore necessary to make certain that these changes do not involve any loss of nutritional value nor the formation of other harmful substances.

Animal experiments

The equipping and staffing of a laboratory to carry out satisfactory toxicological studies on animals needs considerable resources. It is essential to have facilities for housing large numbers of animals and an adequately trained staff to take care of them. In long-term studies, it is important to know the normal life-span of the animals and their liability to natural disease; rats and mice should be from a known strain and in the case of other species the age and previous history should be ascertained, When using rodents, the number of animals should be large enough to allow statistical evaluation of the results. In practice, it is impossible, however, to work with sufficient numbers to ensure detection of the occasional abnormal reactor; reliance must therefore be placed on the majority response to doses several times those recommended for human consumption.

By varying the design and duration of the experiment, different types of information may be obtained. The following types of study are described in the report.

Acute toxicity studies

In these experiments, the substance is administered either orally or parenterally as a single dose and the LD_{50} determined, usually in three different species. If doses greater than 5 g per kg of body-weight produce no deaths, accurate determination of the LD_{50} is considered unnecessary. The animals are kept under observation for 2-4 weeks and the onset, nature and duration of toxic effects noted, as well as the mortality rate. Autopsies are performed on some animals, including some survivors, and

microscopic examination of the tissues is carried out where necessary. Acute toxicity tests enable toxicities of related materials to be compared and may reveal species differences. They should provide sufficient information for the planning of further studies.

Short-term (sub-acute) toxicity studies

In short-term studies, the material under examination is mixed uniformly with the animals' food and administered over a period up to 10% of the normal life-span. A series of experiments is carried out at various dosage levels, including at least one that has no effect and one that produces definite toxic effects. Both rodents and non-rodents should be used, and equal numbers of males and females. Rodents should be taken shortly after weaning to enable the effect on growth to be studied. Any changes in the general appearance and behaviour of the animals should also be noted. In some cases, food intake estimations and biochemical studies may be required. Macroscopic and microscopic examination of the organs should be undertaken, the most important organs for detailed study being in many cases the liver and kidney. Such studies may reveal a possible cumulative action, the nature of the pathological changes, and the approximate dosage level at which these effects occur. They may also provide a guide to a suitable dosage for long-term tests and indicate a need for more extensive investigations. On the other hand, it may be obvious that the substance is too toxic to warrant further study.

Long-term (chronic) toxicity studies

These studies are usually conducted in rats and continued for the major portion of the life-span, i.e., for about two years. To avoid confusion between pathological effects and the normal effects of ageing, however, it is often desirable to terminate the experiments after 12-18 months. On the other hand, for special purposes, total life-span studies extending over two generations may be necessary. In general, the substance is administered with the diet, as in the case of short-term studies, but when testing for a carcinogenic effect parenteral administration may be advantageous. About 25 rats of each sex are used at each dosage level; larger numbers may be needed if it is desired to sacrifice some animals for pathological examination during the experiment. Any adverse effects on reproduction, lactation or the offspring should be noted, in addition to the observations described under short-term studies. A statistically significant difference in weight gain between test and control animals may not be a toxic effect. Anorexia or lack of palatability of the food may be the explanation. Food intake should therefore be checked and paired feeding experiments instituted if necessary. If there are no appreciable differences in food intake, the possibility of impaired absorption or utilization of the food should be examined. Changes in the nutritional value of the food may also have to be considered. Toxic effects may become apparent in these long-term studies which could not be predicted from experiments of shorter duration. The results will indicate the maximum dosage level at which no detectable ill-effects occur when continued for the major portion of the animal's life-span.

Biochemical and other special investigations

In addition to the studies outlined above, it may be profitable to examine certain aspects of the metabolism of the substance under test, such as the route and rate of absorption and excretion, tissue storage, and the nature of the metabolites. Such studies must be done at high dosage levels in the first instance to enable the metabolites to be isolated. Later they should be repeated at levels nearer to those likely to be encountered in practice. Chromatography and radioactive tracer techniques have proved helpful in separating small quantities of metabolites from complex mixtures. Sometimes a minor metabolite proves to be more toxic than the original substance. Other biochemical studies, such as possible interference with enzymatic processes, can also be of value.

Functional tests and macroscopic examination of organs do not always reveal pathological effects, but may indicate the need for more detailed study. Histological studies, on the other hand, are very time-consuming and should be kept to a minimum, though they may provide the earliest evidence of toxicity. The Committee particularly stressed the importance of following up any evidence suggestive of a carcinogenic action, and considered that this question should be given further study at a later date by a group including specialists in cancer research.

Interpretation of results

As in all animal experimentation, great caution must be observed in interpreting the results and deciding their applicability to man. By spreading the tests over several different species, it is possible to extrapolate the result to man, provided that a sufficient safety margin is allowed. It should be assumed that all the foods likely to be treated with the additive will contain it at the proposed level, and on this basis a standard daily dietary dose can be calculated, i.e., the amount of the additive that would be consumed by an average adult eating a normal diet. The committee believed that an arbitrary factor of 100 applied to the experimentally determined maximum "ineffective" dose would constitute an adequate margin of safety. Special consideration might have to be given to substances of very low toxicity.

The Committee recommended that FAO and WHO should give "every possible encouragement" to the continuation and expansion of research into better methods of assessing the safety of food additives. It proposed that the Committee should meet for the purpose of drawing up specifications for the more important food additives; and the possibility of exchanging unpublished information on investigations relating to the use of food additives should be explored.

Health Legislation

MEDICAL SPECIALIZATION: A COMPARATIVE STUDY

Although many studies on post-graduate medical education have been published, they contain very little information about standards for specialist training and requirements for the recognition of specialists in different countries. An extensive survey undertaken by the World Medical Association in 1949 revealed that not many countries had standards for specialist training and that very few of them had embodied these standards in their national legislation.

Since the publication of this survey in 1950, about fifteen countries have enacted legislation on medical specialization or have recast or amended earlier laws on the subject.

This type of legislation is of considerable importance to the medical profession, and the recent publication in the *International Digest of Health Legislation* of a new comparative study [1] of national laws and regulations pertaining to medical specialization is particularly timely.

In general, one of two systems is followed: the regulation of medical specialization by law, or the older, more conservative system whereby the matter is left entirely in the hands of the professional associations and is not subject to legislation. The fact that a relatively large number of countries have enacted legislation on medical specialization in recent years would appear to indicate that the first system is gaining ground. The develop-

[1] See *Int. Dig. Hlth Legis.*, 1957, 8, 562. This study is also available in pamphlet form (price: 1/9, $0.30, or Sw. fr. 1).

ment of medicine in the last fifty years has been marked by a continuous increase in the number of specialists and the number of specialities, and it is therefore understandable that there should be this growing tendency to enact legislation protecting the public against unqualified practitioners or defending the interests of physicians with special medical training. In this connexion, it may be noted that, whereas there were only about ten recognized medical specialities at the beginning of the century, today there are at least fifty. In fact, in some countries, half —or more than half—of the physicians are specialists.

From the study published in the *International Digest of Health Legislation*, it may be seen that the training and recognition of specialists (whether or not as a result of an examination) are the responsibility of the Ministry of National Education, the Ministry of Health, the universities, or the medical associations to which the State delegates certain powers. Specialist training must normally be undergone in duly recognized establishments or institutions, or under the guidance of approved supervisors of studies. A specific period of training is normally laid down for each speciality, although it varies from country to country (for example, for paediatrics the period of training may be from 2 to 5 years: for surgery, from 3 to 6 years; and for ophthalmology, from 2 to 4 years). In some countries—for example, Austria and Denmark—the over-all period of training is stated in general terms, whereas the periods of training to be undergone in the principal, secondary, and complementary branches are specifically prescribed. At the beginning of the century most medical specialists spent several years gaining experience in general practice before devoting themselves exclusively to their chosen speciality. Today, however, general medical experience is no longer required in some countries before specialist training, which begins immediately after graduation. Only partial credit towards the prescribed period of training is given for training acquired abroad.

Recognition may be granted as a result of an examination before a State board of examiners or a group of physicians appointed by the medical association; or it may be granted on the presentation of documents attesting the nature and period of training undergone.

Although laws on medical specialization do not normally stipulate that specialized professional attention be given exclusively by a specialist, they nevertheless contain provisions designed to protect specialist status. The use of more than one specialist designation is, moreover, strictly controlled. From an examination of the pertinent legislation it appears that a certain number of specialities may be practised concurrently; those which may be associated in this way differ from country to country, but in some countries ophthalmology may be practised together with otorhinolaryngology, surgery with neurology, and radiology with radiotherapy.

Many other aspects of medical specialization are dealt with in the study, the subject-matter of which is arranged under the following headings: introduction; laws and regulations; definitions of specialist; specialities and period of training; training requirements; qualifying examinations; certification boards; concurrent practice of specialities; protection of title; refusal of certification or recognition and appeal procedure; registration of specialists; transitional provisions; conclusion; references.

Notes and News

Sensitivity reactions to penicillin

In order to obtain information on the incidence and nature of untoward reactions to penicillin administration, a questionnaire was sent by WHO to members of the WHO Advisory Panel on Venereal Diseases and Treponematoses. Thirty replies were received relating to experience in venereal disease clinics in the Americas, the Eastern Mediterranean, Europe and South East Asia. Figures from 25 centres indicate that at least 2 342 000 persons were treated in the clinics concerned during the period 1952-56. During those years the rates of sensitivity reactions have varied from 0% to 5%, and while there is some suggestion that the incidence is increasing, the evidence is far from conclusive. There was a majority of opinion that reactions were less common in children than in adults and that they were more frequent after repeated injections.

Among 626 551 cases treated in clinics in 17 countries, there were 9 deaths, representing 1 death per 69 600 persons or 0.014 per 1000.

A fuller analysis of the replies received will shortly be published in the *Bulletin of the World Health Organization* in a note by R. R. Willcox.

A detailed study of penicillin reactions in respect of a particular area has also been made. Between October 1951 and May 1955, 106 such reactions were recorded in Taiwan, 74 of them anaphylactic and 32 urticarial; of the anaphylactic reactions, 12 were fatal, 19 were severe and 43 were moderate. This study by O. Idsöe and Wang Ping-Nan will also be published in the WHO *Bulletin*.

The authors point out that the consumption of penicillin is very heavy in Taiwan, which can be considered a "potentially penicillin-sensitized country". The great majority of the anaphylactic cases for which information is available are known to have received penicillin before the injection which caused the reaction, and only one of those who died (a 7-month-old boy) is known not to have had the drug before. All those in the urticarial group for whom there is information reacted within 24 hours of receiving penicillin. The authors conclude that, since this is too short a time for the production of antibodies, the persons concerned were already sensitized by previous penicillin treatment.

Effect of intradermal tuberculin tests on BCG-induced allergy

It is generally accepted that as time goes on there is a spontaneous waning of the allergy produced by BCG vaccination. Certain reports suggest, however, that the annual application of the tuberculin test to schoolchildren (10 TU administered intradermally) prevents this decline of allergy. Because of the absence of data based on a systematic study of the subject, trials with schoolchildren have now been undertaken to determine whether the administration of tuberculin does, in fact, have this "boosting" effect.

In connexion with these studies, K. Magnus of the WHO Tuberculosis Research Office (TRO),[1] has carried out tests on guinea-pigs—the waning of the BCG-induced allergy being more rapid in these animals than in man.

The purpose of this author's first experiment was to ascertain whether the waning of the vaccination-induced allergy, once begun, could be stopped by the intradermal administration of one or several doses of tuberculin and, if so, what doses of tuberculin should be administered. The results obtained confirm that, in the guinea-pig, the decline of the allergy can be prevented by intradermal injection of tuberculin. No statistically significant difference was demonstrated between the effects of the two doses of tuberculin used—5 TU and 100 TU of purified tuberculin. It was noted, moreover, that animals given four injections had lower levels of allergy than those given only one. This

[1] *Bull. Wld Hlth Org.*, 1957, 17, 249

suggests that, side by side with the " boosting " effect, repeated tuberculin tests following vaccination may also cause desensitization.

In his second experiment, Magnus attempted to obtain information on the duration of the allergy-increasing effect of the tuberculin test, and to determine whether the same increase in allergy can be obtained with another type of tuberculin and with smaller doses than those employed in the first experiment.

He found that allergy " boosted " by an intradermal injection of 5 or 100 units of purified tuberculin will slowly wane but is still slightly enhanced after 8 weeks. No boosting effect was observed with the weakest dose of purified tuberculin, 1 TU. Various dilutions of Old Tuberculin also have an enhancing effect.

These experiments have proved that, in the guinea-pig, the application of the tuberculin test can prevent waning of BCG-induced allergy. It remains to be seen whether the same results can be obtained in man, but this will only be known in three to four years, when the studies at present in progress have been completed.

A question which is important from both the theoretical and practical view-points, and to which an answer has still to be found, is: are the tuberculin-induced variations in levels of allergy accompanied by corresponding variations in immunity?

Interpretation of tuberculin reactions

A recent number of the WHO *Bulletin* [1] contains a paper by J. Guld, of the WHO Tuberculosis Research Office (TRO), presenting findings which largely explain apparent fluctuations in the response of BCG-vaccinated persons to tuberculin tests.

In recent years, conflicting results have been observed in tuberculin tests performed at the Central Tuberculosis Dispensary in Copenhagen. After giving a definite reaction in the routine annual tests held to detect cases of recent infection, certain subjects no longer did so when re-tested a little later.

The aim of the investigation reported in the above-mentioned paper was to determine which of the two results—tuberculin-positive or tuberculin-negative—was the correct one, and the causes of the apparent disparity.

A thousand persons, some of them BCG-vaccinated, who were attending the Dispensary for the annual routine examination, were subjected alternately, in the order of their arrival, to one or other of the following tuberculin-test procedures: (*a*) intradermal injection in the forearm of 3 TU, followed on the third day, in the event of the local reaction being less than 13 mm in diameter, by a second injection of 10 TU in the other forearm; (*b*) an injection of 5 TU followed by another, also of 5 TU, if the diameter of the local reaction was less than 15 mm on the third day after the first injection.

An additional study was carried out to investigate the degree of agreement between the results of the tests when the size of the local reaction is measured by different persons.

In a third study, an attempt was made to determine whether the annual repetition of tuberculin tests in the same part of the body can affect the response.

The findings in persons not vaccinated with BCG confirm the general view that tuberculous infection is followed by a uniform degree of tuberculin sensitivity. In practically every person infected with tuberculosis, a test which is carefully carried out with a suitable dose gives a perceptible reaction. Consequently, the term " tuberculin-positive " can be used to designate persons not vaccinated with BCG who give a definite tuberculin reaction, and this response may be considered as due to infection with tuberculosis.

The above applies to Europe and other parts of the world where the sole source of natural sensitivity is infection with *Mycobacterium tuberculosis*. It is known that there are populations in South-East Asia and other tropical regions which show a pronounced, natural non-specific sensitivity. Among such populations a marked reaction to a tuberculin test is not necessarily a proof of tuberculous infection, for the intensity of

[1] *Bull. Wld Hlth Org.*, 1957, 17, 225

such non-specific reactions makes it impossible to differentiate between them and genuinely " positive " tuberculin tests.

In such populations the terms " tuberculin-positive " and " tuberculin-negative " are useless, since, wherever the borderline is traced between " positive " and " negative " and whatever the methods adopted for the tests, the classification will still not correspond to a biological reality.

In BCG-vaccinated persons, the allergy induced by the vaccine can vary quantitatively from person to person over a very wide range. Because of this, the almost universal practice of setting up arbitrary limits between " positive " and " negative " reactions in BCG-vaccinated persons may be a source of confusion and misinterpretation.

There are several factors which explain why tuberculin tests given to the same person in the same way produce different results. They include inaccurate standardization of tuberculin, instability of the dilutions injected, and differences in estimating the size of the reaction. In addition, it must be remembered that repeated intradermal injections in the same area of skin cause local sensitization (the author found a high percentage of accelerated reactions) and a general " booster " effect on allergy.

The classification of BCG-vaccinated persons as either " positive " or " negative " is unrealistic, and has no practical significance. Owing to the existence of the factors mentioned above, the BCG-vaccinated person may be found tuberculin-positive in one test and tuberculin-negative in another, so that there is a danger of arriving at a false conclusion. Thus in some cases it will be considered that the vaccine-induced allergy has disappeared, and in others that a person has become infected with tuberculosis, when, in fact, the allergy has not altered.

Expression of the results of vaccination as percentages of positive and of negative reactions with respect to a given tuberculin dose and on the basis of arbitrary limits —e.g. the size of the local reaction—will doubtless give some information on the degree of sensitivity reached in a group. However, the data thus obtained are much less precise than those based on the average size of the local reaction. Thus, two groups of persons may both be 100% " positive ", yet in one group the local reactions may be much larger than in the other (stronger sensitivity).

As BCG vaccination is at present being carried out on a large scale in many countries, where extensive population groups have been vaccinated, these peculiarities of the tuberculin reaction given by vaccinated persons must be borne in mind in evaluating the results of vaccination and variations in sensitivity in such groups.

Economic losses caused by echinococcosis

Echinococcosis, both human and animal, has serious economic consequences in several European countries where it is prevalent. According to a study by Dr M. Suic in the WHO *Bulletin*,[1] echinococcosis is very widespread in certain parts of Yugoslavia and causes enormous losses in the production of milk, meat and wool. The destruction of infested meat causes a loss of more than 2 000 000 kg every year; furthermore, animals suffering from the disease are thinner, leading to a decrease in production of more than 12 000 000 kg. In addition, infested cattle give less milk; this loss is put at about 116 000 000 l annually. As regards wool production, there is an annual loss of more than 110 000 kg. Animal echinococcosis costs Yugoslavia 7 000 000 000 dinars annually in this way, or nearly $23 000 000. Some idea of the harm done to the national economy by human echinococcosis is given by the cost of hospital treatment and the number of working days lost. The sum involved is 62 000 000 dinars—about $200 000 —per year.

Yugoslav research workers have therefore made an effort to collect relevant epidemiological data, to serve as a guide in taking subsequent measures to eradicate the disease, or at least prevent its spread.

[1] *Bull. Wld Hlth Org.*, 1957, 17, 492

Recent developments in the insecticide-resistance problem

There is little doubt that insecticide-resistance is on the increase. In fact, as was pointed out in July 1956 by a WHO Expert Committee on Insecticides, resistance is developing more rapidly than the necessary measures to deal with it. In view if this, the Committee felt that an international co-operative programme of research on the problem was called for—a programme designed on the one hand to determine the extent of insecticide-resistance throughout the world and on the other to find out more about the origin and mechanism of the various types of resistance. In November 1957, an Expert Committee on Insect Resistance and Vector Control was convened by WHO to review what had been accomplished by this co-operative programme during its sixteen months of operation. The data on which this committee's review was based have been summarized by A. W. A. Brown of the Division of Environmental Sanitation, WHO, in an article that is to appear in a forthcoming number of the *Bulletin of the World Health Organization*.

During the period in question, three new resistant species were discovered (*Anopheles subpictus*, *Chrysomyia putoria* and *Rhipicephalus sanguineus*), while eight species already resistant to one insecticide were observed to have extended their tolerance to others (2 to DDT, 4 to BHC and dieldrin, and 2 to organo-phosphorus compounds). Also, the geographical area covered by resistant populations was found to have increased considerably in the case of 11 of the species examined.

It is not possible to mention here all that has been achieved on the research side.

—Notable advances have been made in the systematization of knowledge of the genetic origins of resistance. DDT-resistance in the housefly, in *Anopheles sundaicus* and in *Aëdes aegypti* has been shown to originate mainly from a single gene and to be associated with the ability to detoxify DDT by dehydrochlorination. Dieldrin-resistance in *Anopheles gambiae* has also been shown to derive from a single gene, whose presence in a certain number of individuals has been demonstrated in field populations even before dieldrin spraying was begun.

—Normal susceptibility levels for a large number of mosquito species have been assessed, so that in future workers will be able to detect resistance as soon as it appears.

—It has been demonstrated that selection pressure from organo-phosphorus compounds in the laboratory will induce moderate resistance to them and high resistance to chlorinated-hydrocarbon insecticides.

—The existence in mosquitos and bed-bugs, as well as in houseflies, of two distinct types of resistance to chlorinated hydrocarbons—one to DDT and its analogues and the other to dieldrin and other cyclodiene derivatives extending to gamma-BHC—has been confirmed.

—Some understanding of the physiological mechanism of BHC-resistance in the housefly has been reached.

—And, finally, the interesting discovery has been made that there are certain chemical compounds which seem to be more toxic to resistant strains of houseflies than to normally susceptible ones. A DDT-susceptible strain has been produced from a DDT-resistant one by submitting the latter to selection pressure from an impure sample of a certain organo-phosphorus compound for three generations. If the same can be done in the case of resistant strains of other insects of public-health importance, it may be possible to work out a practical means of counteracting insecticide-resistance.

A promising outlook for malaria eradication in Southern Rhodesia

With increasing efforts being devoted the world over to the eradication of malaria, and, simultaneously, with an ever-growing number of reports being received that certain vector mosquitos are showing varying degrees of resistance to insecticides, it is of no little interest to be reminded that positive results are nevertheless being achieved in very many countries. Dr William Alves, Director of

the Malaria and Bilharziasis Research Laboratory at Salisbury, Southern Rhodesia, reports that a recent survey in that country shows that, following seven years of insecticide spraying, the malaria parasite rate among the indigenous population is now so low that for practical purposes a break in malaria transmission may have been achieved. Should this indeed prove to be so, the continued use of chloroquine as a suppressive may no longer be justified and the large-scale application of insecticides may now be unnecessary.

There remains, however, a dangerous potential source of infection in the immigrants from other territories seeking employment in Southern Rhodesia. Measures have therefore been taken at several points of entry to dose immigrants with tablets containing 150 mg of amodiaquine and 15 mg of primaquine.

A full account of Dr Alves's findings will appear in a forthcoming issue of the *Bulletin of the World Health Organization.*

It may be added that, in response to a request from the Government, WHO is sending to Southern Rhodesia a malariologist and an entomologist for a period of 18 months to review the situation and to make recommendations to the Government.

Meeting on malaria eradication

A meeting on malaria eradication was held in Baghdad, under WHO auspices, from 7 to 12 December. It was attended by malariologists from Cyprus, Egypt, Iran, Iraq, Jordan, Lebanon, Pakistan, Saudi Arabia, Somalia and Syria, as well as representatives from WHO Headquarters, Geneva, and the WHO Regional Office for the Eastern Mediterranean, Alexandria. Observers were present from UNICEF, UNRWA, the US International Co-operation Administration, and the Rockefeller Foundation.

In the course of the meeting, the progress of malaria eradication in the Eastern Mediterranean Region was reviewed and plans were made for the co-ordination of the future malaria eradication activities of the countries and territories represented. The standardization of methods of operating and reporting, in order to achieve maximum efficiency and comparability of results, was also discussed. Papers by specialists in various aspects of malaria control and eradication were used as a basis for discussion. The recent development of DDT resistance in *A. stephensi* in Iran and Iraq was brought to the attention of the meeting, and ways and means of solving this important problem were discussed.

Division of Malaria Eradication established at WHO Headquarters

On 1 December 1957, a Division of Malaria Eradication, directed by Dr E. J. Pampana, was established in the Department of Advisory Services at WHO Headquarters, Geneva. The functions of the new Division are to advise on malaria eradication policies and techniques, and to direct and co-ordinate all the malaria activities of the Organization. The Division has a Planning Section, and a Programme Section which includes a Malaria Intelligence Unit. Dr E. B. Weeks has been appointed Chief of the Programme Section.

The Planning Section will give advice and assistance on plans of operation, research work and pilot projects. It will also be responsible for the supervision of pre-eradication survey teams and special advisory and research teams.

The Programme Section will follow the progress of eradication programmes, providing technical guidance and advice on any difficulties that may arise. It will also deal with matters relating to the recruitment and training of staff for malaria eradication, and will act as the secretariat for the Expert Committee on Malaria. The Malaria Intelligence Unit will be concerned with the collection and circulation of technical information on malaria eradication, including progress reports on eradication programmes throughout the world.

US contribution of $7 million to malaria eradication funds

At a ceremony in the State Department, Washington, D.C., in December, Mr J. Foster Dulles, US Secretary of State,

presented a cheque for $5 million to Dr M. G. Candau, Director-General of WHO, as a voluntary contribution from the US Government to the WHO Special Account for Malaria Eradication. On the same occasion, Mr Dulles presented a cheque for $2 million to Dr Fred Soper, Director of the Pan American Sanitary Bureau, which acts as the WHO Regional Office for the Americas, for the Special Malaria Fund of that region.

In presenting these cheques, Mr Dulles said: " ... malaria has left a trail of personal tragedy, adverse effects on industry, agriculture, education and economic progress. Our own nation has suffered acutely from this disease. Until recent years malaria cost the United States over $500 million yearly and unmeasurable human misery. Our country has now rid itself of this scourge, but today more than 600 million people in the world are still exposed to this killing, debilitating disease." Mr Dulles went on to express the agreement of the United States with WHO's goal of malaria eradication, adding : " If the world does not immediately seize this opportunity, [it] may well be lost... The campaign must be completed before the malaria-carrying mosquito becomes resistant to modern insecticides."

The WHO Special Account for Malaria Eradication was set up in 1955 to receive voluntary contributions from governments and private sources, for malaria research purposes and to provide equipment, supplies and services for the eradication of the disease.

Review of WHO Publications

THERAPEUTIC AND DIAGNOSTIC SUBSTANCES

Bulletin of the World Health Organization, 1957, Volume 17, Numbers 4-5 (pages 517-864)

International collaboration on drugs and biological substances has its roots in the latter part of the nineteenth century; since then, an extremely complex network of activities has grown up. For the World Health Organization, this has involved work in such varied spheres as, to name but a few, the standardization of, and the proposal of recommended requirements for, biological substances; the establishment of an international pharmacopoeia; the proposal of internationally acceptable non-proprietary names for drugs; the collection and dissemination of information on the production and use of food additives; the development of internationally recommended laboratory methods; the establishment of requirements for the postal transmission of virus preparations and other potentially dangerous substances; and the international control of addiction-producing drugs.

A number of papers illustrating several facets of this activity were published in 1954 in the *Bulletin of the World Health Organization* under the title *Therapeutic, Prophylactic, and Diagnostic Substances*. The present issue brings together a new collection of such papers, covering a somewhat narrower range of subjects.[1]

The first four papers are from the Department of Biological Standards, National Institute for Medical Research, London, which holds the International Standards for pharmacological substances. Two of these articles describe the newly established International Standards for Tetracycline and Erythromycin, defining the International Unit for each. The other two are concerned with assay methods.

[1] For the list of contents, see the advertising section at the end of this issue of the *Chronicle*.

In one a precise assay of diphtheria toxin is described, based on the linear relationship between the logarithm of the toxin dose and the diameter of the skin response. It eliminates the need for preliminary titrations, is economical, provides information about the slope of the log-dose response lines and, therefore, of the validity of the assay, and yields limits of error of potency from the internal evidence of the assay. In the other a new method is given for the assay of penicillin in blood-serum, using *Sarcina lutea* as the test organism; this method makes it possible for fiducial limits of the estimated potencies to be readily computed.

By a resolution adopted in 1953, at its sixteenth session, the United Nations Economic and Social Council invited the World Health Organization to prepare information on the addictive properties and therapeutic advantages of synthetic as compared with natural narcotics, the status of scientific knowledge on the relationship between the chemical structure of a drug and its addictive properties, and the relationship between the strongly analgesic qualities of a drug and its addiction-producing properties. This invitation was made to WHO as one of the four organs concerned with the international control of addiction-producing drugs, the others being the Commission on Narcotic Drugs of the Economic and Social Council, the Permanent Central Opium Board, and the Drug Supervisory Body. The Commission on Narcotic Drugs, a policy-making body composed of the representatives of fifteen governments, makes recommendations as to the means by which the control of narcotic drugs may be improved. The Permanent Central Opium Board is made up of eight experts appointed by the Economic and Social Council; the Board studies the statistics on the licit narcotics traffic and suggests measures to be taken where governments fail to comply with international agreements. The Drug Supervisory Body reviews yearly each Member State's requirements in narcotic drugs; it is composed of four experts, two appointed by WHO, one by the Permanent Central Opium Board, and one by the Commission on Narcotic Drugs. Finally, WHO acts in an advisory capacity—to the other international narcotics control organs as well as to governments—on the medical aspects of addiction and of addiction-producing drugs. In accordance with the resolution of the Economic and Social Council a series of studies has been prepared on synthetic substances with morphine-like effect. Three of these have been published in earlier numbers of the *Bulletin of the World Health Organization*. The fourth, dealing with clinical experience on potency, side-effects and addiction liability, makes up the bulk of the present issue.

VIRUS DISEASES

Bulletin of the World Health Organization, 1957, Volume 17, Number 6 (pages 865-1056)

This issue of the *Bulletin*[1] comprises articles on two of the neurotropic virus diseases (poliomyelitis and rabies) which have lately been thrown into prominence—on the one hand by the urgent need to avert an increasing threat of communicable infection, and on the other under the stimulus of innovations in treatment and prophylaxis. Before the Second World War the Health Organization of the League of Nations sponsored the collection of much information on these diseases, tracking and investigating outbreaks of poliomyelitis, and putting forward proposals for the international control of rabies. It is only during the past decade, however, that fundamental large-scale research, in particular on human immunization, could be pursued with all the impetus of improved laboratory techniques and increased understanding of immunity mechanisms derived from work on other virus and bacterial diseases.

In 1950 and 1953 respectively, the World Health Organization convened Expert Committees on Rabies and Poliomyelitis to examine the existing state of knowledge and

[1] For the list of contents, see the advertising section at the end of this issue of the *Chronicle*.

to define general programmes of research. Since then, at several sessions recommendations have been made in both fields on methods of diagnosis, study of the virus, and the production and application of vaccines and sera. Members of the WHO Expert Advisory Panels on Rabies and Poliomyelitis, together with other collaborating workers, have proceeded on the basis of these recommendations, and the results are reported in many of the papers in this number of the *Bulletin*. In addition, two monographs have been published—one to provide guidance on acceptable and uniform laboratory techniques for use in rabies work, the other a reference book on the diagnosis and treatment of poliomyelitis. Two special numbers of the *Bulletin* have also appeared, devoted respectively to recent developments in rabies research and prophylaxis, and to a consideration of resemblances between virus meningo-encephalitis and poliomyelitis. Successful control of these diseases must inevitably be based upon the laboratory, and the contributions included in the present issue of the *Bulletin* show that much work of this nature is in progress.

Workers in the USA have contributed two experimental studies on antirabies immunization of man with HEP Flury, Harris-type and Semple-type vaccines given in different dosages; these papers are complemented by a further report from an international team on antibody response to different schedules of serum and vaccine inoculations in non-exposed persons. Another American worker, using mice, explores the interference phenomenon noted in human rabies prophylaxis. One paper from the Pasteur Institute of Southern India describes a method for the preparation of lyophilized rabies street virus material for challenge; another reports an experimental evaluation of serum, vaccine, and combined methods of rabies treatment in guinea-pigs challenged with Indian street virus. The results of the compulsory mass canine vaccination campaigns in Malaya are brought up to date in a brief note. Different methods of local treatment of wounds caused by rabid animals are discussed in a contribution from a Spanish laboratory.

The production of "killed" poliovirus vaccines demands a thorough understanding of the structure of the virus itself, as well as of the kinetics of reaction between it and the chemical agent; this highly topical problem is considered in an article from Sweden dealing with the inactivation of poliovirus by formaldehyde. Two French workers present a comparative serological study of poliomyelitis and encephalomyelitis antibodies in certain population groups. A Canadian research team describes observations on the use of dialysed vaccine for tissue-culture safety testing of Salk vaccines. Finally, an account is given of the methods used in Israel to produce safe and effective polio vaccine on a semi-industrial scale.

MALARIA

WHO Malaria Conference for the Eastern Mediterranean and European Regions (1957) *Report* (*World Health Organization: Technical Report Series*, No. 132), 47 pages.
Price: 3/6, $0.60, Sw. fr. 2. Also published in French and Spanish.

This report deals with the Malaria Conference for the Eastern Mediterranean and European Regions, held in June 1956, in Athens. It includes an analysis of the problems encountered by the antimalaria services of the countries concerned, as well as suggestions for technical, administrative and financial measures to hasten the eradication of the disease in the two Regions. A summary of the work of the Conference will be found in an earlier issue of the *Chronicle*.[1]

[1] *Chron. Wld Hlth Org.*, 1956, **10**, 354

CORRIGENDUM

Vol. 11, No. 10

MAN'S SPIRITUAL AND SCIENTIFIC LEGACY FROM ROSS

Page 303, right-hand column, line 8,
for Piyoth *read* Pinotti

THERAPEUTIC AND DIAGNOSTIC SUBSTANCES

Introduction

International Standard for Tetracycline—*J. H. Humphrey, J. W. Lightbown & Marjorie V. Mussett*

International Standard for Erythromycin—*J. H. Humphrey, J. W. Lightbown & Marjorie V. Mussett*

The assay of diphtheria toxin—*Julia Gerwing, D.A. Long & Marjorie V. Mussett*

The assay of penicillin in blood-serum using *Sarcina lutea*—*J. W. Lightbown & D. Sulitzeanu*

Synthetic substances with morphine-like effect. Clinical experience: potency, side-effects, addiction liability—*Nathan B. Eddy, H. Halbach & Olav J. Braenden*

BULLETIN OF THE WORLD HEALTH ORGANIZATION

Vol. 17, No. 4-5, 348 pages

Price: £1; $4.00; Sw. fr. 12.—

VIRUS DISEASES

Introduction

Studies of antirabies immunization of man: Observations with HEP Flury and other vaccines, with and without hyperimmune serum, in primary and recall immunizations—*John P. Fox, Hilary Koprowski, Donald P. Conwell, Jack Black & Henry M. Gelfand*

Preliminary observations in primary antirabies immunization of man with different types of high-egg-passage Flury virus—*George R. Sharpless, Jack Black, Herald R. Cox & James M. Ruegsegger*

Rabies neutralizing antibody response to different schedules of serum and vaccine inoculations in non-exposed persons: Part II—*P. Atanasiu, M. Bahmanyar, M. Baltazard, J. P. Fox, K. Habel, M. M. Kaplan, R. E. Kissling, A. Komarov, H. Koprowski, P. Lépine, F. Pérez Gallardo & M. Schaeffer*

Rabies antiserum interference with antigenicity of vaccine in mice—*Karl Habel*

Preparation of lyophilized rabies street virus material from infective submaxillary glands for challenge purposes—*N. Veeraraghavan*

Advances in rabies treatment: An experimental evaluation—*N. Veeraraghavan, A. Balasubramanian & T. P. Subrahmanyan*

Local treatment of wounds to prevent rabies—*F. Pérez Gallardo, E. Zarzuelo & M. M. Kaplan*

Inactivation of poliovirus by formaldehyde: Theoretical and practical aspects—*Sven Gard*

Position particulière des encéphalomyélites de type Mengo par rapport aux poliomyélites: Répartition d'anticorps spécifiques chez certaines populations d'Afrique centrale et d'autres zones géographiques—*G. Barski & Francine Cornefert*

Production of formalinized poliomyelitis vaccine (Salk-type) on a semi-industrial scale—*N. Goldblum, Tamar Gotlieb & G. Miller*

Rabies control in Malaya, August 1952-October 1956—*C. W. Wells*

Some observations on tissue-culture safety testing of Salk polio vaccines—*F. P. Nagler. R. E. Armstrong & R. C. French*

Bibliographical section

BULLETIN OF THE WORLD HEALTH ORGANIZATION

Vol. 17, No. 6, 192 pages

Price: 10/-; $2.00; Sw. fr. 6.—.

WORLD HEALTH *ORGANIZATION*

INTERNATIONAL DIGEST OF HEALTH LEGISLATION

Separate editions in English and in French

The *International Digest of Health Legislation*, published quarterly, is the only periodical devoted solely to the publication of health legislation of international significance. It contains a selection of health legislation reproduced in full, published in extract form, summarized, or mentioned by title. In addition, comparative studies of legislation on special subjects are included, and are also available as separate brochures.

Price per number	12/–	$2.25	Sw.fr. 7.—
Annual subscription	£2	$7.50	Sw.fr. 25.—

COMPARATIVE HEALTH LEGISLATION (Offprints)

NURSING			
(from Vol. 4, No. 4) 35 pages	2/–	$0.25	Sw.fr. 1.—
LEPROSY			
(from Vol. 5, No. 1) 33 pages	1/9	$0.25	Sw.fr. 1.—
SMALLPOX VACCINATION			
(from Vol. 5, No. 2) 40 pages	3/6	$0.50	Sw.fr. 2.—
MIDWIVES			
(from Vol. 5, No. 3) 52 pages	3/6	$0.50	Sw.fr. 2.—
HOSPITALIZATION OF MENTAL PATIENTS			
(from Vol. 6, No. 1) 100 pages	6/9	$1.25	Sw.fr. 4.—
CONTROL OF INSECT VECTORS IN INTERNATIONAL AIR TRAFFIC			
(from Vol. 6, No. 3) 59 pages	3/6	$0.70	Sw.fr. 2.—
VENEREAL DISEASES			
(from Vol. 7, No. 2) 44 pages	3/6	$0.70	Sw.fr. 2.—
MALARIA			
(from Vol. 7, No. 4) 32 pages	1/9	$0.30	Sw.fr. 1.—
DIPHTHERIA IMMUNIZATION			
(from Vol. 8, No. 2) 27 pages	1/9	$0.30	Sw.fr. 1.—
MEDICAL SPECIALIZATION			
(from Vol. 8, No. 4) 37 pages	1/9	$0.30	Sw.fr. 1—